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Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria

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ABSTRACT

BACKGROUND

Up-regulation of hepatic delta-aminolevulinic acid synthase 1 (ALAS1), with resultant accumulation of delta-aminolevulinic acid (ALA) and porphobilinogen, is central to the pathogenesis of acute attacks and chronic symptoms in acute hepatic porphyria. Givosiran, an RNA interference therapy, inhibits ALAS1 expression.

METHODS

In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned symptomatic patients with acute hepatic porphyria to receive either subcutaneous givosiran (2.5 mg per kilogram of body weight) or placebo monthly for 6 months. The primary end point was the annualized rate of composite porphyria attacks among patients with acute intermittent porphyria, the most common subtype of acute hepatic porphyria. (Composite porphyria attacks resulted in hospitalization, an urgent health care visit, or intravenous administration of hemin at home.) Key secondary end points were levels of ALA and porphobilinogen and the annualized attack rate among patients with acute hepatic porphyria, along with hemin use and daily worst pain scores in patients with acute intermittent porphyria.

RESULTS

A total of 94 patients underwent randomization (48 in the givosiran group and 46 in the placebo group). Among the 89 patients with acute intermittent porphyria, the mean annualized attack rate was 3.2 in the givosiran group and 12.5 in the placebo group, representing a 74% lower rate in the givosiran group ($P<0.001$); the results were similar among the 94 patients with acute hepatic porphyria. Among the patients with acute intermittent porphyria, givosiran led to lower levels of urinary ALA and porphobilinogen, fewer days of hemin use, and better daily scores for pain than placebo. Key adverse events that were observed more frequently in the givosiran group were elevations in serum aminotransferase levels, changes in serum creatinine levels and the estimated glomerular filtration rate, and injection-site reactions.

CONCLUSIONS

Among patients with acute intermittent porphyria, those who received givosiran had a significantly lower rate of porphyria attacks and better results for multiple other disease manifestations than those who received placebo. The increased efficacy was accompanied by a higher frequency of hepatic and renal adverse events. (Funded by Alnylam Pharmaceuticals; ENVISION ClinicalTrials.gov number, NCT03338816.)

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*A list of the ENVISION investigators is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Acute hepatic porphyria is a family of rare genetic disorders that is caused by defects in heme biosynthesis enzymes.[1,2] Acute intermittent porphyria is the most common subtype of this disorder and accounts for approximately 80% of all symptomatic cases.[3-5] Other, rarer types of acute hepatic porphyria include hereditary coproporphyria, variegate porphyria, and delta-aminolevulinic acid (ALA) dehydratase–deficiency porphyria.[2,6,7] Mutations in the gene that causes acute intermittent porphyria are relatively common (approximately 1 in 1600 white persons); however, disease penetrance (development of symptoms) among mutation carriers is approximately 1% in the general population and up to 50% in families with a history of the disorder.[8,9]

In patients with acute hepatic porphyria, induction of hepatic ALA synthase 1 (ALAS1) results in the accumulation of neurotoxic heme intermediates, including ALA and porphobilinogen (PBG).[1,10-12] The accumulation of ALA and possibly PBG causes injury to the nervous system and other organs, resulting in potentially life-threatening acute attacks and chronic disease manifestations.[1,10-12] This disease has been associated with long-term coexisting illnesses, including chronic kidney disease, hypertension, chronic neuropathy, and liver disease (manifested as elevated aminotransferase levels, fibrosis, cirrhosis, and hepatocellular carcinoma); these complications have been attributed to long-term elevated levels of ALA and PBG.[3,6,13-19] In addition, patients may have iron overload from repeated hemin treatment.[20]

Attacks that occur in acute hepatic porphyria are more commonly seen in females and are characterized by severe, diffuse abdominal pain, along with muscle weakness, autonomic neuropathy (e.g., hypertension, tachycardia, nausea, vomiting, and constipation), and changes in mental status.[3,15,21] Attacks typically warrant urgent medical attention and sometimes prolonged hospitalization and rehabilitation.[1,15,21] Current options for managing attacks include the removal of triggering factors and treatment with intravenous opioids, glucose, and hemin.[12,21] Most symptomatic patients have only a few attacks in their lifetime, but up to 8% have recurrent attacks (defined in some cases as four or more attacks per year).[18] Treatment options for preventing attacks are limited and include hormone-suppression therapy, off-label prophylactic hemin, and, in rare cases, liver transplantation.[7,21,22]

Givosiran is a subcutaneously administered RNA interference therapeutic targeting hepatic ALAS1 messenger RNA (mRNA), thereby preventing the accumulation of ALA and PBG (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[23] Givosiran is conjugated to a trivalent *N*-acetylgalactosamine ligand, which binds specifically to the asialoglycoprotein receptor, enabling targeted delivery to hepatocytes.[24,25]

In a phase 1–2 trial, givosiran treatment led to rapid and sustained lowering of hepatic levels of ALAS1 mRNA and urinary levels of ALA and PBG, along with a lower porphyria attack rate than placebo, in patients with acute intermittent porphyria who were having ongoing attacks.[26,27] Here, we report the efficacy and safety results from ENVISION, a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial involving patients with acute hepatic porphyria with ongoing attacks.

METHODS

TRIAL OVERSIGHT

The trial was designed by the sponsor, Alnylam Pharmaceuticals, in collaboration with the academic authors. The protocol was approved by a central or local institutional review board or ethics committee at each trial center. The trial was conducted in accordance with Good Clinical Practice guidelines of the International Conference on Harmonisation and the provisions of the Declaration of Helsinki. All the patients provided written informed consent.

An independent data and safety monitoring committee reviewed all pertinent safety data. Data were collected by trial investigators and staff members and analyzed by the sponsor. Medical writers who were employed by the sponsor prepared the first draft of the manuscript, with editorial assistance provided by Adelphi Communications under contract with Alnylam Pharmaceuticals. All the authors interpreted the data, collaborated in the preparation of the manuscript and the decision to submit it for publication, and vouch for the accuracy and completeness of the data and for the fidelity of

the trial to the protocol, which is available at NEJM.org. All the authors, their institutions, and the sponsor were required to maintain data confidentiality during the trial.

PATIENTS

Key eligibility criteria included an age of at least 12 years, a diagnosis of acute hepatic porphyria, an elevated level of urinary ALA or PBG (≥4 times the upper limit of the normal range [ULN]), and either a confirmed pathogenic mutation associated with acute hepatic porphyria or biochemical and clinical criteria consistent with a diagnosis of acute hepatic porphyria if such a mutation was not identified on genetic testing. (The determination of the ULN for ALA [1.5 mmol per mole of creatinine] and for PBG [0.14 mmol per mole of creatinine] was based on samples obtained from 150 healthy persons.[15]) Patients were required to have documentation of at least two composite porphyria attacks (i.e., resulting in hospitalization, urgent health care, or intravenous administration of hemin at home) within 6 months before baseline. Patients were also required to discontinue or not initiate prophylactic hemin during the trial. Details regarding the eligibility requirements are provided in the protocol and the Supplementary Appendix.

TRIAL DESIGN AND REGIMEN

Patients were enrolled at 36 sites in 18 countries and randomly assigned in a 1:1 ratio to receive monthly givosiran (at a dose of 2.5 mg per kilogram of body weight) or placebo[26] for 6 months. Randomization was stratified according to the subtype of acute hepatic porphyria (acute intermittent porphyria with an identified mutation vs. any another subtype [hereditary coproporphyria, variegate porphyria, ALA dehydratase–deficiency porphyria with an identified mutation, or acute hepatic porphyria without an identified mutation]), previous use or nonuse of hemin prophylaxis, and a high or low annualized attack rate in the previous 12 months (<7 attacks [low] vs. ≥7 attacks [high] among patients who were receiving hemin prophylaxis at baseline and <12 attacks [low] vs. ≥12 attacks [high] among those who were not receiving hemin prophylaxis). Investigators treated attacks according to the local standard of care, which could include intravenous administration of hemin.

OUTCOME MEASURES AND SAFETY ASSESSMENTS

The primary end point was the annualized rate of composite porphyria attacks (annualized attack rate) among patients with acute intermittent porphyria during the 6-month intervention period. Secondary end points were urinary ALA levels (at 3 and 6 months); urinary PBG levels (at 6 months) in patients with acute intermittent porphyria; the annualized number of days of hemin use in patients with acute intermittent porphyria; the annualized attack rate among all patients with acute hepatic porphyria; daily worst scores for pain, fatigue, and nausea in patients with acute intermittent porphyria; and the change from baseline in the score on the Physical Component Summary of the 12-Item Short-Form Health Survey, version 2 (SF-12), in patients with acute intermittent porphyria.[28] Daily worst scores for pain, fatigue, and nausea were measured on a numerical rating scale ranging from 0 to 10, with higher scores indicating more severe symptoms. Scores on the Physical Component Summary of the SF-12 range from 0 (worst functioning) to 100 (best functioning), with 2 to 5 points representing a clinically meaningful difference, according to published data for other chronic diseases.[29,30] Key exploratory end points were the use of analgesics as recorded at baseline and daily during the intervention period, findings on the Patient Global Impression of Change[31] regarding the change in overall status since the start of the trial, and results on the Porphyria Patient Experience Questionnaire regarding the change in the perceived treatment experience and in the ability to function and perform activities of daily living at 6 months. Safety assessments included monitoring of adverse events and laboratory assessments. (Details regarding the end points and safety assessments are provided in the Supplementary Appendix.)

STATISTICAL ANALYSIS

We estimated that the enrollment of 74 patients would provide a power of at least 90% to detect a relative lowering of 45% in the annualized attack rate in the givosiran group at a two-sided 5% significance level, assuming a mean (±SD) annualized attack rate of 8±5 in the placebo group. The analysis population was the full analysis set, including all the patients who had undergone randomization and received at least

one dose of givosiran or placebo. The primary end point and most secondary efficacy end points were assessed in patients with acute intermittent porphyria with an identified mutation to allow for a more homogeneous population for an assessment of efficacy.[5]

The primary analyses of the annualized attack rate and number of days of hemin use were based on a negative binomial regression model adjusted according to the use of hemin prophylaxis and the historical annualized attack rate. The analyses of longitudinal secondary efficacy end points were based on a mixed model for repeated measures. For the end points capturing daily worst scores for pain, fatigue, and nausea, we calculated the area under the curve of change during the 6-month intervention period on the basis of the change from baseline in weekly mean scores. When the normality assumption was violated, a nonparametric Wilcoxon signed-rank test was conducted to reanalyze the data. Secondary end points were analyzed in a prespecified hierarchical order to control for the overall type I error.[32] The handling of missing data is described in the statistical analysis plan, available in the protocol.

RESULTS

TRIAL POPULATION

From November 16, 2017, through June 27, 2018, a total of 94 patients with 64 different genotypes were enrolled; during randomization, 48 patients were assigned to receive givosiran and 46 to receive placebo (Fig. S2). All the patients completed the 6-month visit. The baseline characteristics of the patients were generally balanced in the two groups (Table 1). The mean (±SD) age was 38.8±11.4 years; 89% of the patients were female.

Of the 94 patients, 89 had acute intermittent porphyria. Among the other subtypes of acute hepatic porphyria, 1 patient had hereditary coproporphyria, 2 had variegate porphyria, and 2 had acute hepatic porphyria without an identified mutation; both the patients with the last subtype were subsequently assessed by the investigator as having acute intermittent porphyria on the basis of biochemical analysis (Table S1).

The median historical annualized attack rate among all the patients was 8 (interquartile range, 4 to 16). Baseline levels of ALA and PBG were similar in the two randomized groups and were markedly elevated above the ULN (see the Supplementary Appendix).[15] According to the patients' medical histories, their coexisting illnesses included increased aminotransferase levels (in 37%), iron overload (in 33%), liver disease (in 28%), hypertension (in 27%), and renal impairment (in 25%). At baseline, 34% of the patients had an estimated glomerular filtration rate (eGFR) of less than 60 ml per minute per 1.73 m^2 of body-surface area.

EFFICACY

Primary End Point

In patients with acute intermittent porphyria, the mean annualized rate of composite porphyria attacks over 6 months was 3.2 (95% confidence interval [CI], 2.3 to 4.6) in the givosiran group and 12.5 (95% CI, 9.4 to 16.8) in the placebo group, representing a 74% lower rate in the givosiran group (P<0.001) (Fig. 1A). For each of the three components of the composite attacks, there was a greater reduction in the givosiran group than in the placebo group. The median annualized attack rate was 1.0 (interquartile range, 0.0 to 6.2) in the givosiran group and 10.7 (interquartile range, 2.2 to 26.1) in the placebo group, a relative difference of 90% (Fig. 1B). This decrease was evident within the first month and was sustained throughout the intervention period (Fig. S3). Fifty percent of the patients in the givosiran group had no porphyria attacks during the intervention period, as compared with 17% of those in the placebo group (Fig. S4). A prespecified subgroup analysis showed a consistent effect of givosiran on the annualized attack rate across all nine demographic and clinical subgroups (Fig. S5).

Secondary End Points

The key secondary end points are shown in Table 2. Among the patients with acute intermittent porphyria, levels of urinary ALA (at 3 and 6 months) and PBG (at 6 months) were significantly lower in the givosiran group than in the placebo group (P<0.001). Reductions were sustained throughout the intervention period (Fig. 1C and 1D); in the givosiran group, the median percent reduction from baseline at 6 months was 86% for urinary ALA levels and 91% for PBG levels.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Patients with Acute Hepatic Porphyria			Patients with Acute Intermittent Porphyria		
	Placebo (N=46)	Givosiran (N=48)	Overall (N=94)	Placebo (N=43)	Givosiran (N=46)	Overall (N=89)
Age — yr	37.4±10.5	40.1±12.1	38.8±11.4	37.3±10.5	40.7±12.0	39.0±11.4
Female sex — no. (%)	41 (89)	43 (90)	84 (89)	39 (91)	41 (89)	80 (90)
Body-mass index†	25.5±6.4	24.3±5.2	24.9±5.8	25.7±6.3	24.3±5.2	24.9±5.8
Race — no. (%)‡						
White	34 (74)	39 (81)	73 (78)	33 (77)	37 (80)	70 (79)
Black	1 (2)	0	1 (1)	0	0	0
Asian	7 (15)	8 (17)	15 (16)	6 (14)	8 (17)	14 (16)
Other	4 (9)	1 (2)	5 (5)	4 (9)	1 (2)	5 (6)
Acute intermittent porphyria with identified mutation — no. (%)	43 (93)	46 (96)	89 (95)	43 (100)	46 (100)	89 (100)
Nonacute intermittent porphyria§						
All subtypes	3 (7)	2 (4)	5 (5)	NA	NA	NA
Hereditary coproporphyria	0	1 (2)	1 (1)			
Variegate porphyria	1 (2)	1 (2)	2 (2)			
Acute hepatic porphyria without identified mutation	2 (4)	0	2 (2)¶			
No. of yr since diagnosis	8.3±8.5	11.1±11.2	9.7±10.0	8.4±8.7	11.5±11.3	10.0±10.2
Previous hemin prophylaxis — no. (%)						
Yes	18 (39)	20 (42)	38 (40)	17 (40)	20 (43)	37 (42)
No	28 (61)	28 (58)	56 (60)	26 (60)	26 (57)	52 (58)
Historical annualized attack rate‖						
High — no. (%)	21 (46)	24 (50)	45 (48)	20 (47)	23 (50)	43 (48)
Low — no. (%)	25 (54)	24 (50)	49 (52)	23 (53)	23 (50)	46 (52)
Median rate (IQR)	7 (4–14)	8 (4–18)	8 (4–16)	8 (4–14)	8 (4–18)	8 (4–16)
Previous chronic symptoms — no. (%)**						
Yes	26 (57)	23 (48)	49 (52)	24 (56)	22 (48)	46 (52)
No	20 (43)	25 (52)	45 (48)	19 (44)	24 (52)	43 (48)
Previous long-term opioid use — no. (%)††						
Yes	13 (28)	14 (29)	27 (29)	12 (28)	14 (30)	26 (29)
No	33 (72)	34 (71)	67 (71)	31 (72)	32 (70)	63 (71)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and NA not applicable.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Race was reported by the investigator after discussion with the patient.

§ Porphyria subtypes other than acute intermittent porphyria include hereditary coproporphyria, variegate porphyria, delta-aminolevulinic acid (ALA) dehydratase–deficiency porphyria with an identified mutation, and acute hepatic porphyria without an identified mutation. No patients with ALA dehydratase–deficiency porphyria were enrolled in this trial.

¶ The two patients with acute hepatic porphyria without an identified mutation were considered by the trial investigator to have acute intermittent porphyria on the basis of biochemical analysis.

‖ The historical annualized attack rate was calculated as the number of attacks resulting in a composite of hospitalization, a visit to a health care facility, or hemin use at home during the 6 months before randomization. For patients who were receiving hemin prophylaxis before the initiation of the trial, the attack rate was considered to be high if the historical annualized attack rate was 7 or more and low if the attack rate was less than 7 (attack rate of ≥12 and <12, respectively, for patients who were not receiving previous hemin prophylaxis). One patient in the placebo group did not meet the inclusion criterion of a history of at least 2 composite porphyria attacks, since the patient had 2 attacks that were treated at home without intravenous hemin, which was identified as a protocol deviation.

** Symptoms were considered to be chronic if patients had symptoms of porphyria daily or on most days when they were not having an attack, as reported by the investigator. Information was reported on a screening questionnaire administered by trial staff members.

†† Opioid use was defined as long-term if patients reported taking an opioid for porphyria daily or most days when they were not having an attack, as reported on the screening questionnaire.

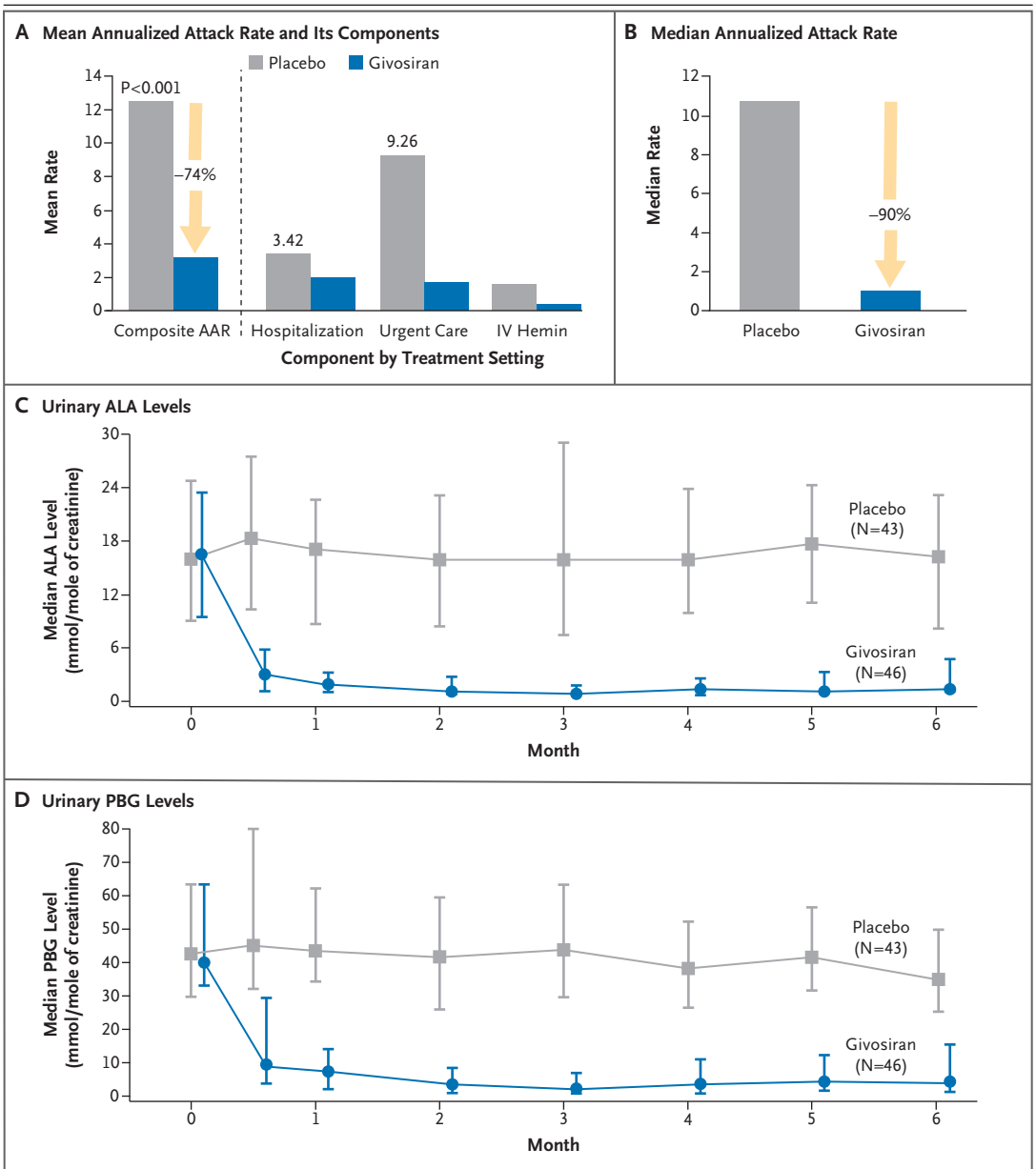

Figure 1. Annualized Attack Rate (AAR) and Urinary Levels of Neurotoxic Heme Intermediates in Patients with Acute Intermittent Porphyria.

Panel A shows the mean annualized rate of composite porphyria attacks (the primary end point) among the 89 patients with acute intermittent porphyria who received either givosiran or placebo. A composite porphyria attack was defined as an attack that resulted in hospitalization, an urgent health care visit, or intravenous administration of hemin at home. IV denotes intravenous. Panel B shows the median annualized attack rate, which was calculated from the individual patients' annualized attack rates. Also shown are the median levels of urinary delta-aminolevulinic acid (ALA) (Panel C) and porphobilinogen (PBG) (Panel D) in patients with acute intermittent porphyria. In Panels C and D, the I bars denote the interquartile range.

In patients with acute intermittent porphyria, the mean annualized number of days of hemin use was significantly lower in the givosiran group than in the placebo group at 6 months (6.8 days vs. 29.7 days, representing a 77% lower number in the givosiran group) (P<0.001). Over-

Table 2. Secondary Efficacy End Points.*

Secondary End Points	Placebo (N=43)	Givosiran (N=46)	Difference†	P Value
Urinary ALA — mmol/mole of creatinine				
Mean (±SD) level at baseline	17.5±10.9	20.0±16.8		
Month 3				
Least-squares mean (±SE)	20.0±1.5	1.8±1.4	−18.2±2.0	<0.001
Median (IQR)	15.7 (7.5 to 28.9)	0.8 (0.5 to 1.7)	−14.6 (−18.0 to 9.6)‡	<0.001
Month 6				
Least-squares mean (±SE)	23.2±2.5	4.0±2.4	−19.1±3.5	<0.001
Median (IQR)	16.2 (8.0 to 23.0)	1.3 (0.9 to 4.6)	−12.8 (−16.1 to −7.8)‡	<0.001
Urinary porphobilinogen — mmol/mole of creatinine				
Mean (±SD) at baseline	46.8±24.3	50.4± 34.3		
Least-squares mean (±SE) at 6 mo	49.1±5.0	12.9±4.6	−36.2±6.8	<0.001
Median (IQR) at 6 mo	35.1 (25.6 to 50.0)	4.4 (1.6 to 15.3)	−27.5 (−34.0 to −21.0)‡	<0.001
Annualized no. of days of hemin use				
Mean (95% CI)	29.7 (18.4 to 47.9)	6.8 (4.2 to 10.9)	0.23 (0.11 to 0.45)§	<0.001
Median (IQR)¶	27.6 (2.1 to 47.6)	0.0 (0.0 to 10.8)		
Annualized attack rate in patients with acute hepatic porphyria				
Mean (95% CI)	12.3 (9.2 to 16.3)	3.4 (2.4 to 4.7)	0.27 (0.17 to 0.43)§	<0.001
Median (IQR)¶	10.7 (2.2 to 25.9)	1.0 (0.0 to 6.4)		
Daily worst score for pain‖				
Median of change in AUC from baseline (IQR)	5.3 (−23.0 to 11.1)	−11.5 (−29.2 to 3.0)	−10.1 (−22.8 to 0.9)‡	0.046
Median of average change from baseline (IQR)	0.2 (−1.0 to 0.5)	−0.5 (−1.3 to 0.1)	−0.4 (−1.0 to 0.1)‡	0.049
Daily worst score for fatigue‖				
Least-squares mean (±SE) of change in AUC from baseline	−4.2±4.7	−11.1±4.5	−6.9±6.5	NS
Least-squares mean (±SE) of average change from baseline	−0.2±0.2	−0.5±0.2	−0.3±0.3	NS
Daily worst score for nausea‖				
Least-squares mean (±SE) of change in AUC from baseline	−4.0±3.5	1.5±3.3	5.5±4.8	NT
Least-squares mean (±SE) of average change from baseline	−0.2±0.2	0.1±0.1	0.2±0.2	NT
SF-12**				
Mean (±SD) at baseline	38.4±9.4	39.4±9.6		NT
Least-squares mean (±SE) of change from baseline at 6 mo	1.4±1.2	5.4±1.2	3.9±1.7	NT

* All secondary end points are reported in patients with acute intermittent porphyria for time points during the 6-month intervention period unless otherwise stated. ALA denotes delta-aminolevulinic acid, AUC area under curve, CI confidence interval, and NS not significant. Statistical significance was not tested (NT) if the end point did not meet the conditions of the prespecified hierarchical order.

† Differences are for the givosiran group, as compared with the placebo group.

‡ Because of a significant deviation from normal distribution, the planned methods of a mixed model for repeated measures or analysis of covariance were not valid. A nonparametric stratified Wilcoxon signed-rank test was therefore conducted. The median of the between-group difference was estimated with the use of the Hodges–Lehmann method.

§ This value is a rate ratio (95% CI) for the comparison between givosiran and placebo.

¶ The between-group difference in the median values in this category was not calculated with the use of statistical models.

‖ Scores for pain, fatigue, and nausea were measured on a numerical rating scale ranging from 0 to 10, with higher scores indicating more severe symptoms.

** Scores on the Physical Component Summary of the 12-Item Short-Form Health Survey, version 2 (SF-12), range from 0 (worst functioning) to 100 (best functioning), with published literature in other chronic diseases suggesting that a change of 2 to 5 points represents a clinically meaningful difference.

all, 54% of the patients in the givosiran group had no days of hemin use, as compared with 23% of those in the placebo group. Among all the patients with acute hepatic porphyria, the mean annualized attack rate was significantly lower in the givosiran group than in the placebo group at 6 months, representing a 73% lower rate in the givosiran group (P<0.001) (Table S2). Among the patients with acute intermittent porphyria, the worst daily pain score was significantly lower in the givosiran group than in the placebo group (P=0.046 by post hoc Wilcoxon signed-rank test) (Fig. S6). There were no significant between-group differences in the worst daily scores for fatigue or nausea.

Among the patients with acute intermittent porphyria, the mean (±SE) change from baseline in the Physical Component Summary of the SF-12 was 3.9±1.7 points higher (indicating improvement) in the givosiran group than in the placebo group at 6 months. Results across SF-12 domains showed a consistent effect favoring givosiran over placebo, with the largest effects regarding bodily pain, social functioning, and role limitations due to physical problems (Fig. S7).

Exploratory End Points

The percentage of patients with acute intermittent porphyria who used any opioids during the trial period was 67% in the givosiran group and 88% in the placebo group; the median percentage of days of opioid use during the intervention period was 3.0% (interquartile range, 0.0 to 38.5) and 10.8% (interquartile range, 2.4 to 83.3), respectively. On the Patient Global Impression of Change at 6 months in patients with acute hepatic porphyria, the percentage that rated overall health status as either "much improved" or "very much improved" was 59% in the givosiran group and 18% in the placebo group. On the Porphyria Patient Experience Questionnaire in patients with acute hepatic porphyria, the percentage who had improvements from baseline in their ability to function and perform activities of daily living and in treatment satisfaction was larger in the givosiran group than in the placebo group (Fig. S8A and S8B).

SAFETY

Adverse events are listed in Table 3. Overall, adverse events were reported by 90% of the patients in the givosiran group and 80% of those in the placebo group. Adverse events that were reported more frequently in the givosiran group than in the placebo group were injection-site reactions, nausea, chronic kidney disease, decreased eGFR, rash, increased alanine aminotransferase (ALT) levels, and fatigue.

The percentage of serious adverse events was higher in the givosiran group than in the placebo group (21% vs. 9%) (Table S3). The difference in serious adverse events was not driven by any particular event. Serious adverse events that were reported in at least 2 patients were worsening of chronic kidney disease (in 2 patients in the givosiran group) and events consistent with central venous catheter infection (in 1 patient in the givosiran group and 2 patients in the placebo group). One patient in the givosiran group discontinued treatment because of abnormal results on liver-function testing; this occurrence was reported as a serious adverse event. There were no deaths.

Hepatic adverse events, as characterized by elevations in serum aminotransferase levels, were more frequent in the givosiran group than in the placebo group (Tables S4 and S5). An ALT level of more than 3 times the ULN was reported in 7 patients (15%) in the givosiran group and in 1 (2%) in the placebo group. These increases occurred primarily 3 to 5 months after the initiation of givosiran and placebo; all the events were reported as hepatic adverse events except for one in a patient in the givosiran group who had a history of nonalcoholic steatohepatitis, in whom the investigator considered that the elevated ALT level was consistent with previous values. In the givosiran group, for 1 patient who had an ALT elevation of 9.9 times the ULN, the abnormal results on liver-function testing were reported as a serious adverse event; in this case, the patient permanently discontinued treatment with givosiran, in accordance with the stopping rules prespecified in the protocol. The elevation resolved with normal ALT values at 6 months. No other adverse events led to treatment discontinuation or withdrawal from the trial. In 1 patient with an ALT elevation of 5.4 times the ULN, the administration of givosiran was temporarily interrupted, in accordance with the protocol-specified dosing rule, and was resumed at a lower dose (1.25 mg per kilogram) after resolution, without recurrence of the ALT elevation. The other 5 patients who had an ALT level of more

Table 3. Adverse Events in All Trial Patients.*

Adverse Events	Placebo (N=46)	Givosiran (N=48)
	no. of patients (%)	
Any adverse event	37 (80)	43 (90)
Any severe adverse event	5 (11)	8 (17)
Any serious adverse event	4 (9)	10 (21)
Any adverse event leading to discontinuation of the trial regimen	0	1 (2)
Death	0	0
Adverse events with higher frequency (≥5 percentage points) in the givosiran group		
Injection-site reaction†	0	12 (25)
Nausea	5 (11)	13 (27)
Chronic kidney disease	0	5 (10)
Decreased eGFR	0	3 (6)
Rash	0	3 (6)
Increased alanine aminotransferase	1 (2)	4 (8)
Fatigue	2 (4)	5 (10)
Adverse events with higher frequency (≥5 percentage points) in the placebo group		
Pyrexia	6 (13)	1 (2)
Hypoesthesia	4 (9)	0
Dyspepsia	4 (9)	0
Vomiting	5 (11)	2 (4)
Urinary tract infection	6 (13)	3 (6)
Back pain	4 (9)	1 (2)
Adverse events of interest		
Hepatic‡	1 (2)	6 (13)
Renal§		
Any event	3 (7)	7 (15)
Increased serum creatinine or decreased eGFR¶	2 (4)	7 (15)

* Serious adverse events were defined as adverse events that resulted in death, were life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, were a congenital anomaly or birth defect, or were important medical events as determined by the investigators. All adverse events (including serious adverse events) were graded for severity. Severe events were adverse events for which more than minimal, local, or noninvasive intervention was indicated; had a more severe effect on limiting self-care activities of daily living; or had potential for life-threatening consequences or death.

† Injection-site reactions include all adverse events that are included under the term of high-level injection-site reactions in the *Medical Dictionary for Regulatory Activities* (MedDRA).

‡ Hepatic adverse events included elevated aminotransferase levels, which occurred in each of the 7 patients in the givosiran group and were selected according to MedDRA terms for drug-related hepatic disorders.

§ Renal adverse events included all events selected according to MedDRA terms for chronic kidney disease.

¶ This category includes a subgroup of patients who had changes in the serum creatinine level or estimated glomerular filtration rate (eGFR) that were reported as an increased blood creatinine level, a decreased eGFR, chronic kidney disease, or nephropathy.

than 3 times the ULN had resolution of the ALT elevations with continued dosing (at 2.5 mg per kilogram). Elevations of serum aminotransferase levels were seen at similar frequencies and degrees in patients with or without elevated aminotransferase levels at baseline.

Renal adverse events were reported in 15% of the patients in the givosiran group and in 7% of

those in the placebo group (Table S6); the majority of these events were an increase in the serum creatinine level or a reduction in the eGFR. Of these events, 5 patients in the givosiran group had either the onset or worsening of chronic kidney disease (Table S7), and 1 patient in the placebo group had worsening nephropathy, all of which were associated with an increased creatinine level and a decreased eGFR. Two patients in the givosiran group who had worsening of chronic kidney disease (which was reported as a serious adverse event) had renal-biopsy results that were consistent with their underlying coexisting illnesses (hypertension and porphyria-associated nephropathy). No patients discontinued either givosiran or placebo because of a renal adverse event.

Overall, an analysis of renal measures showed that increases in the serum creatinine level (median increase at 3 months, 0.07 mg per deciliter [6.2 μmol per liter]) and corresponding decreases in the eGFR (Fig. S9) were noted early during givosiran treatment; both findings were mainly reversible over time without any dose modifications. Stratification of patients according to the baseline category of eGFR did not show an increased percentage of renal impairment (as assessed by the eGFR) in any group.

Injection-site reactions occurred in 25% of the patients in the givosiran group and were associated with 7% of 279 givosiran doses. All the reactions were mild or moderate in severity, and none led to discontinuation. There were no clinically significant elevations in amylase or lipase levels and no development of antidrug antibodies. (Details regarding all adverse advents are provided in the Supplementary Appendix.)

DISCUSSION

Patients who have acute hepatic porphyria with ongoing attacks have a severe disease burden and limited treatment options. In such patients, we found that a givosiran-mediated reduction in hepatic ALAS1 mRNA resulted in a sustained lowering of heme intermediates ALA and PBG, which are thought to cause the manifestations of this disorder.[1,11,12] To ensure a homogeneous, enriched population for an evaluation of the efficacy of givosiran, we assessed the primary end point and most secondary end points in patients with genetically confirmed acute intermittent porphyria, the most common subtype of acute hepatic porphyria.

Among 89 such patients, the annualized rate of composite porphyria attacks (the primary end point) was 74% lower in the givosiran group than in the placebo group; among 94 patients with acute hepatic porphyria, the rate was 73% lower — differences that were both significant and clinically meaningful. Such between-group differences were observed within the first month of treatment and were sustained throughout the intervention period, with 50% of patients having no porphyria attacks while they were receiving givosiran. A consistent effect on the annualized attack rate was observed across all nine prespecified subgroups, which showed the extent of the treatment effect. Givosiran treatment in patients with acute intermittent porphyria also led to sustained reductions in levels of ALA and PBG, with beneficial effects across a broad range of acute and chronic disease manifestations. These effects were shown by secondary and exploratory efficacy measures that included hemin use, daily worst pain, analgesic use, physical functioning, overall health and well-being, activities of daily living, and treatment satisfaction, as compared with placebo. More than 50% of the patients in the givosiran group did not receive any hemin infusions during the trial. Such reductions in hemin use may be beneficial, since hemin is potentially associated with both acute side effects (e.g., headache, fever, and phlebitis) and chronic side effects (e.g., iron overload, venous obliteration, and complications with indwelling central venous catheters).[17,20,33]

The cardinal symptom of acute hepatic porphyria, neuropathic pain, is often refractory to treatment and requires complex analgesic regimens.[6,34,35] Givosiran-treated patients with acute intermittent porphyria had better daily pain scores and less analgesic use than those who received placebo. Improvements in physical health status and in the bodily pain domain of the SF-12 may suggest that the observed better scores for pain were clinically relevant. Although between-group differences in daily scores for worst fatigue and nausea were not observed during the 6-month treatment period, the trial was not specifically enriched for patients with high baseline scores for chronic symptoms.

The main safety finding was elevations in serum aminotransferase levels, which were re-

ported primarily during the 3 to 5 months after initiation of the trial regimen. Most patients with elevations had resolution with continued administration of givosiran, which suggests adaptation by the liver. Of the patients with ALT values of more than three times the ULN, most had a medical history of liver disease (e.g., porphyria-related liver disease, increased aminotransferase levels, and iron overload). No patients with an elevated ALT level had concomitant elevations in levels of total bilirubin of more than two times the ULN.

Chronic kidney disease is a commonly recognized coexisting illness and long-term complication of acute hepatic porphyria,[13,15] and approximately one third of patients in the trial had a reduced eGFR (<60 ml per minute per 1.73 m^2) at baseline. There was a greater frequency of renal adverse events, as characterized by an increased serum creatinine level and associated decreases in the eGFR, with givosiran than with placebo. The mechanism of these changes is unknown. The results of analyses of renal-biopsy samples obtained from two patients with chronic kidney disease and hypertension were consistent with the patients' underlying coexisting illnesses and showed no signs of an adverse drug effect (e.g., acute tubular toxicity, immune complexes, and glomerulonephritis). Overall, increased levels of serum creatinine and decreases in the eGFR occurred early during the 6-month period and were mostly transient and reversible. Renal function should be monitored during givosiran treatment, as clinically indicated.

It has been hypothesized that decreasing ALAS1 expression could lead to hepatic heme deficiency and affect the activity of heme-dependent enzymes (e.g., cytochrome P450 [CYP]). In a drug–drug interaction study involving patients with acute intermittent porphyria who were not having porphyria attacks, givosiran was associated with a moderate effect on CYP1A2 and CYP2D6, a weak effect on CYP2C19 and CYP3A4, and no effect on CYP2C9.[36] These results suggest that givosiran does not have a strong effect on hepatic heme content or heme-dependent enzyme activity.

Limitations of this trial include the 6-month duration of the intervention period. Data from an ongoing phase 1–2 open-label extension study of givosiran (median duration, 26 months) have shown sustained reductions in the annualized attack rate, in levels of ALA and PBG, and in hemin use.[27] In addition, limited data were obtained in patients with subtypes of acute hepatic porphyria other than acute intermittent porphyria because of the extreme rarity of such patients who have ongoing attacks. Our findings suggest that patients with all subtypes of acute hepatic porphyria would probably derive similar clinical benefits from givosiran, since the subtypes have common pathophysiological features and treatment, along with the reduced levels of ALA and PBG seen in the givosiran-treated patients with hereditary coproporphyria and variegate porphyria. We are currently evaluating the long-term efficacy and safety of givosiran during the open-label extension period of the ENVISION trial involving patients with all subtypes of acute hepatic porphyria.

Thus, in the ENVISION phase 3 trial, we found that patients with acute intermittent porphyria who received givosiran for 6 months had a significantly lower annualized rate of porphyria attacks and better results regarding multiple other disease manifestations than those who received placebo. The use of givosiran was associated with an acceptable safety profile, although patients had a higher frequency of hepatic and renal adverse events. On the basis of these results, givosiran was approved for the treatment of acute hepatic porphyria in adults by the Food and Drug Administration on November 20, 2019, and by the European Medicines Agency (EMA) on March 3, 2020; the EMA also approved the use of givosiran in adolescents older than 12 years of age.[37,38]

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APPENDIX

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